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(54) Title: USE OF INHALED NO AS ANTI-INFLAMMATORY AGENT (57) Abstract <p>A method for lessening or preventing non-pulmonary ischemia-reperfusion injury or inflammation in a mammal by identifying a mammal which has ischemia-reperfusion or is at risk for developing ischemia-reperfusion in a non-pulmonary tissue; and causing the mammal to inhale a therapeutically effective amount of gaseous nitric oxide sufficient to diminish the ability of leukocytes or platelets to become activated in a manner that contributes to an inflammatory process at the site of the ischemia-reperfusion or inflammation in the non-pulmonary tissue, thereby lessening or preventing non-pulmonary ischemia-reperfusion injury in the mammal.</p>		

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USE OF INHALED NO AS ANTI-INFLAMMATORY AGENT

Statement as to Federally Sponsored Research

Work on this invention was supported, in part,
5 with funds from the United States government (USPHS
grants HL66377, HL42397, and HL45895). The government
therefore has certain rights in the invention.

Field of the Invention

The field of the invention is treatment of
10 ischemia-reperfusion injury and inflammation.

Background of the Invention

Nitric oxide (NO) is a cell membrane-permeable,
free radical molecule which accounts for the vasodilator
activity of endothelium-derived relaxing factor (reviewed
15 in Schmidt et al., Cell 78:919-925 [1994]). NO interacts
with several intracellular molecular targets, one of
which is soluble guanylate cyclase (sGC). Binding of NO
to the heme group in sGC stimulates the conversion of
guanosine triphosphate (GTP) to guanosine-3',5'-cyclic
20 monophosphate (cGMP). cGMP exerts its effects on cells,
in part, through its action on cGMP-dependent protein
kinase (cGDPK). Additional cGMP targets include
cGMP-gated ion channels and cGMP-regulated cyclic
nucleotide phosphodiesterases. Phosphodiesterases (PDEs)
25 inactivate cGMP by converting it to GMP. At least four
types of PDEs appear to participate in the metabolism of
cyclic nucleotides in non-ocular tissues (types 1-3 and
5), only one of which, type 5 (PDE5), is specific for
cGMP metabolism. Several agents act as selective
30 inhibitors of PDE5, including dipyridamole and
Zaprinast™.

The biological effects of NO are also mediated by
cGMP-independent mechanisms. NO can serve as an
antioxidant, opposing the effect of superoxides. The

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antioxidant properties of NO appear to account for its ability to modulate proinflammatory activation of endothelial cells. NO may also react with superoxide to form peroxynitrite which may be responsible for the cellular toxicity associated with high levels of NO production.

NO decreases the adherence and aggregation of platelets exposed to a variety of stimuli. This has been demonstrated in vitro and in vivo (Adrie et al., Circulation 94:1919-1926 [1996]). The effect of NO on platelet function appears to be mediated by cGMP and is augmented by PDE5 inhibitors (see PCT application WO96/25184, which is incorporated herein by reference).

The use of NO as a drug is complicated by evidence suggesting that high levels of NO can contribute to cell injury (Nicholson et al., Trends Pharmacol Sci 12:19-27 [1991]). This is, at least in part, mediated by the combination of NO with reactive oxygen intermediates to form peroxynitrite which decomposes to toxic NO_2^+ and OH^- . NO contributes to neuronal cell injury associated with cerebral ischemia (Iadecola, Trends Neurosci 20:132-139 [1997]). In addition, NO inhibits myocardial contractility and stimulates apoptosis of cardiac myocytes (Wu et al., J Biol Chem 272:14860-14866 [1997]), thereby impairing cardiovascular function. NO also contributes to inflammation in arthritis and possibly other autoimmune diseases when present at the site of inflammation (Nicholson et al., Id.).

NO inhibits adherence of neutrophils to endothelium, an effect which may depend on mast cells (Niu et al., Circ Res 79:992-999 [1996]).

Summary of the Invention

It has been discovered that inhaled gaseous nitric oxide can act on both platelets and leukocytes, affecting

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them in a way that leaves them less likely to be activated once they reach a tissue susceptible to inflammation. The effect on platelets and leukocytes presumably occurs while they are in the pulmonary
5 circulation, since NO itself is rapidly inactivated by hemoglobin once it contacts the blood (Rich et al., J Appl Physiol 75:1278-1284 [1993] and Rimar et al., Circulation 88:2884-2887 [1993]) and so likely does not travel to distal sites of inflammation.

10 Accordingly, the invention relates to a method for lessening or preventing non-pulmonary ischemia-reperfusion injury in a mammal. The method includes identifying a mammal (e.g., a human) that has ischemia-reperfusion or is at risk for developing ischemia-
15 reperfusion in a non-pulmonary tissue, and causing the mammal to inhale a therapeutically effective amount of gaseous nitric oxide. This amount is sufficient to diminish the ability of circulating leukocytes or platelets to become activated and contribute to an
20 inflammatory process at the site of ischemia-reperfusion in the non-pulmonary tissue. This lessens or prevents non-pulmonary ischemia-reperfusion injury in the mammal. In combination with the inhaled NO gas, the mammal can be administered a therapeutically effective amount of a
25 second compound that potentiates the therapeutic effect of gaseous NO. The second compound can be, for example, a phosphodiesterase inhibitor (e.g., 2-o-propoxyphenyl-8-azapurin-6-one [Zaprinast™], dipyridamole, theophylline, sildenafil [Viagra™, Pfizer], or 1,3-dimethyl-6-[2-
30 propoxy-5-methanesulphonylamidophenyl]-pyrazolo[3,4-D]pyrimidin-4-[5H]-one) or superoxide dismutase. The second compound can alternatively be an antithrombotic agent such as ticlopidine, streptokinase, urokinase, t-PA or an analog thereof (e.g., met-t-PA, Retevase™, or
35 FE1X), heparin, hirudin or an analog thereof (e.g.,

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Hurulog™), non-steroidal anti-inflammatory agent (e.g., indomethacin or aspirin), a glucocorticoid (e.g., prednisone), or a cytotoxic agent (e.g., methotrexate); or an anti-leukocyte agent such as an anti-leukocyte
5 antibody.

The method is used to treat or prevent ischemia-reperfusion injury including those caused by surgery (e.g., transplantation surgery [especially kidney or heart transplantation surgery] or heart bypass surgery),
10 thrombolysis, stroke, trauma-induced temporary hypotension, or a vascular interventional procedure such as atherectomy or angioplasty including the use of a laser, balloon, or stent. The method can be used to treat or prevent ischemia-reperfusion injury after
15 percutaneous transluminal coronary angioplasty. The injury treated or prevented can occur in any non-pulmonary tissue, including the kidney, heart, or brain.

The invention also features a method for decreasing or preventing non-pulmonary inflammation in a
20 mammal. Examples of non pulmonary inflammation are arthritis, myocarditis, encephalitis, transplant rejection, systemic lupus erythematosus, gout, dermatitis, inflammatory bowel disease, hepatitis, or thyroiditis. This method includes the steps of
25 identifying a mammal which has existing inflammation or is at risk for developing inflammation in a non-pulmonary tissue; causing the mammal to inhale a therapeutically effective amount of gaseous nitric oxide sufficient to diminish the ability of circulating leukocytes or
30 platelets to become activated in a manner that contributes to an inflammatory process in the non-pulmonary tissue, thereby decreasing or preventing non-pulmonary inflammation in the mammal; and administering to the mammal a therapeutically effective amount of a
35 second compound that potentiates the anti-inflammatory

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effect of inhaled gaseous nitric oxide. The second compound can be a phosphodiesterase inhibitor (e.g., 2-o-propoxyphenyl-8-azapurin-6-one [Zaprinast™], dipyridamole, theophylline, sildenafil [Viagra™, Pfizer],
5 or 1,3-dimethyl-6-[2-propoxy-5-methanesulphonylamidophenyl]-pyrazolo[3,4-D]pyrimidin-4-[5H]-one) or superoxide dismutase. The second compound can alternatively be an anti-inflammatory drug such as a non-steroidal anti-inflammatory agent (e.g., indomethacin
10 or aspirin), a glucocorticoid (e.g., prednisone), or a cytotoxic agent (e.g., methotrexate).

The NO gas inhaled by the mammal in the method of this invention can be administered at a predetermined concentration. Preferably it is administered in the
15 absence of tobacco smoke. Preferably the predetermined concentration is 0.1 ppm to 300 ppm, more preferably 1 ppm to 250 ppm, and most preferably 5 ppm to 200 ppm. NO can be inhaled continuously or intermittently for an extended period, i.e., for at least 24 hours.

20 As used herein "preventing" an injury means preventing at least part of the injury, and does not imply that 100% of the injury is prevented. Injury prevented is ischemia-reperfusion injury or inflammation. As used herein, injury "occurs spontaneously," means that
25 the injury has no readily observable cause.

As used herein, "potentiating the therapeutic effect of gaseous nitric oxide," (by a second compound) means increasing the duration or magnitude of the effect.

As used herein, "vascular interventional
30 procedure" means any surgical procedure that involves an anatomical disruption or a mechanical disturbance of a blood vessel.

Other features and advantages of the present invention will be apparent from the following detailed
35 description and also from the claims.

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Detailed Description of the Invention

This invention relates to methods of treating or preventing ischemia-reperfusion injury or inflammation through inhalation of nitric oxide gas. The methods are
5 simple and rapid, affect non-pulmonary tissues, and do not lead to NO-associated cytotoxicity in non-pulmonary tissues.

Without further elaboration, it is believed that one skilled in the art can, based on the above disclosure
10 and the description below, utilize the present invention to its fullest extent. The following description is to be construed as merely illustrative of how one skilled in the art can treat or prevent ischemia-reperfusion injury or inflammation in non-pulmonary tissues using inhaled
15 nitric oxide, and does not limit the remainder of the disclosure in any way. Any publications cited in this disclosure are hereby incorporated by reference.

Administration of Inhaled NO

Inhaled NO is preferably administered from a
20 source of stored, compressed NO gas. Compressed NO gas may be obtained from a commercial supplier such as Ohmeda, typically as a mixture of 200-800 ppm NO in pure N₂ gas. The source of NO can be 100% NO, or diluted with N₂ or any other inert gas (e.g., helium). It is vital
25 that the NO be obtained and stored as a mixture free of any contaminating O₂ or higher oxides of nitrogen, because such higher oxides of nitrogen (which can form by reaction of O₂ with NO) are potentially harmful to lung tissues. If desired, purity of the NO may be
30 demonstrated with chemiluminescence analysis, using known methods, prior to administration to the patient. Chemiluminescence NO-NO_x analyzers are commercially available (e.g., Model 14A, Thermo Environmental Instruments, Franklin, MA). The NO-N₂ mixture may be

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blended with air or O₂ through, for example, calibrated rotameters which have been validated previously with a spirometer. The final concentration of NO in the breathing mixture may be verified with a chemical or
5 chemiluminescence technique well known to those in the field (e.g., Fontijin et al., Anal Chem 42:575 [1970]). Alternatively, NO and NO₂ concentrations may be monitored by means of an electrochemical analyzer. Any impurities such as NO₂ can be scrubbed by exposure to NaOH solutions,
10 baralyme, or sodalime. As an additional control, the FiO₂ of the final gas mixture may also be assessed. Optionally, the ventilator can have a gas scavenger added to the expiratory outlet to ensure that significant amounts of NO do not escape into the adjacent
15 environment.

In a hospital or emergency field situation, administration of NO gas can be accomplished, for example, by attaching a tank of compressed NO gas in N₂, and a second tank of oxygen or an oxygen/N₂ mixture, to an
20 inhaler designed to mix gas from two sources. By controlling the flow of gas from each source, the concentration of NO inhaled by the patient can be maintained at an optimal level. NO can also be mixed with room air, using a standard low-flow blender (e.g.,
25 Bird Blender, Palm Springs, CA). NO can be generated from N₂ and O₂ (i.e., air) by using an electric NO generator. A suitable NO generator is described in Zapol, U.S. Patent No. 5,396,882. In addition, NO can be provided intermittently from an inhaler equipped with a
30 source of NO such as compressed NO or an electric NO generator. The use of an inhaler may be particularly advantageous if a second compound (e.g., a phosphodiesterase inhibitor) is administered, orally or by inhalation, in conjunction with the NO.

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NO can be administered to a mammal identified as having a non-pulmonary ischemia-reperfusion injury or inflammation, or a mammal identified as being at risk for developing a non-pulmonary ischemia-reperfusion injury or inflammation. Preferably, the NO concentration is 0.1 ppm to 300 ppm in air, pure oxygen, or another suitable gas or gas mixture. The NO can be administered for as long as needed. The concentration can be temporarily increased for short periods of time, e.g., 5 min at 200 ppm NO. This can be done when an immediate effect is desired.

For treatment or prevention of non-pulmonary ischemia-reperfusion injury or inflammation, inhaled NO can be administered by nasal prongs, mask, tent, intra-tracheal catheter or endotracheal tube, for an extended period, i.e., days or weeks. The administration can be continuous, during the extended period. Alternatively, administration can be intermittent during the extended period. The administration of gaseous NO can be via spontaneous or mechanical ventilation.

Assessment of Effects of Inhaled NO

When inhaled NO is administered, it is desirable to monitor the effects of the NO inhalation. Such monitoring can be used, in a particular individual, to verify desirable effects and to identify undesirable side effects that might occur. Such monitoring is also useful in adjusting dose level, duration and frequency of administration of inhaled NO in a given individual.

Other Agents Administered with NO

NO decomposes rapidly by reacting with molecular oxygen to produce nitrite and nitrate. In addition, NO entering the blood is rapidly inactivated by tight binding to hemoglobin. For these reasons, NO has only a

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short half-life in arterial blood. This means that inhaled NO advantageously avoids systemic vasodilation, an undesirable, potentially dangerous side effect associated with sustained systemic NO release from NO
5 donor compounds such as nitroglycerin.

It may be desirable to prolong the beneficial effects of inhaled NO within leukocytes or platelets, or within cells interacting with the leukocytes or platelets in the lung. In determining how to prolong the
10 beneficial effects of inhaled NO, it is useful to consider that one of the in vivo effects of NO is activation of soluble guanylate cyclase, which stimulates production of cGMP. At least some of the beneficial effects of NO may result from its stimulation of cGMP
15 biosynthesis. Accordingly, in some embodiments of the invention, a phosphodiesterase inhibitor is administered in conjunction with NO inhalation to inhibit the breakdown of cGMP by endogenous phosphodiesterases.

The phosphodiesterase inhibitor can be introduced
20 into the mammal by any suitable method, including via an oral, transmucosal, intravenous, intramuscular, subcutaneous or intraperitoneal route. Alternatively, the inhibitor can be inhaled by the mammal. For inhalation, the phosphodiesterase inhibitor is
25 advantageously formulated as a dry powder or an aerosolized or nebulized solution having a particle or droplet size of less than 10 μm for optimal deposition in the alveoli, and may optionally be inhaled in a gas containing NO.

30 A suitable phosphodiesterase inhibitor is Zaprinast™ (M&B 22948; 2-o-propoxyphenyl-8-azapurine-6-one; Rhone-Poulenc Rorer, Dagenham Essex, UK). Zaprinast™ selectively inhibits the hydrolysis of cGMP with minimal effects on the breakdown of adenosine
35 cyclic-monophosphate in vascular smooth muscle cells

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(Trapani et al., J Pharmacol Exp Ther 258:269 [1991]; Harris et al., J Pharmacol Exp Ther 249:394 [1989]; Lugnier et al., Biochem Pharmacol 35:1743 [1986]; Souness et al., Br J Pharmacol 98:725 [1989])). When using
5 ZaprinstTM according to this invention, the preferred routes of administration are intravenous or oral. The suitable dose range may be determined by one of ordinary skill in the art. A stock solution of ZaprinstTM may be prepared in 0.05 N NaOH. The stock can then be diluted
10 with Ringer's lactate solution to the desired final ZaprinstTM concentration, immediately before use.

In a preferred embodiment, the NO is administered at 20 ppm in air for 45 min. At the start of the 45 min period, 1.0 mg of ZaprinstTM per kg body weight is
15 administered over 4 min, followed by a continuous infusion of 0.004 mg/kg/min for the rest of the 45 min period. Alternatively, at the start of the 45 min period, 0.15 mg dipyridamole per kg body weight is administered over 4 min, followed by a continuous
20 infusion of 0.004 mg/kg/min for the rest of the 45 min period. The ZaprinstTM or dipyridamole are administered in a saline solution. In addition, the methods are not limited to co-administration of only one drug. For example, the administration of either phosphodiesterase
25 inhibitor above can be augmented by administration of a superoxide dismutase.

This invention can be practiced with other phosphodiesterase inhibitors. Various phosphodiesterase inhibitors are known in the art, including dipyridamole
30 and theophylline. A suitable route of administration and suitable dose range can be determined by one of ordinary skill in the art.

Antithrombotic agents can be administered together with NO in accordance with the invention. Such
35 antithrombotic agents serve to (1) restore perfusion of

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the tissues susceptible to ischemia-reperfusion injury via thrombolysis, and (2) augment the therapeutic effects of inhaled NO by decreasing the potential for activation of platelets in non-pulmonary tissues. Examples of
5 antithrombotic agents are aspirin, streptokinase, urokinase, tissue plasminogen activator ("t-PA"), met-t-PA (i.e., t-PA with an N-terminal methionine residue), FE1X (a t-PA analog), heparin, hirudin, Hirulog™ (a hirudin analog), ticlopidine, and IIb/IIIa (e.g.
10 Rheopro™). Other antithrombotic agents could also be used in the practice of this invention. One or more such antithrombotic agents may be administered to a mammal before, during, or after treatment with inhaled NO, so that the potential of platelets to become activated in
15 non-pulmonary tissues is decreased.

In addition, one or more anti-leukocyte agents (e.g., anti-leukocyte antibodies) can be administered in the methods of this invention. Such agents can be administered with inhaled NO with or without
20 antithrombotic agents. When both anti-leukocyte agents and antithrombotic agents are administered along with NO, such agents can augment the therapeutic effect of NO by further decreasing the potential activation of both leukocytes and platelets in the non-pulmonary tissue
25 susceptible to ischemia-reperfusion injury or inflammation.

The selection of appropriate antithrombotic and/or anti-leukocyte agents to be administered in conjunction with inhaled NO, and the selection of the appropriate
30 dosage and route of administration of those antithrombotic agents, is within ordinary skill in the art.

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What is claimed is:

1. A method for lessening or preventing non-pulmonary ischemia-reperfusion injury in a mammal, comprising the steps of:

5 (a) identifying a mammal that has ischemia-reperfusion or is at risk for developing ischemia-reperfusion in a non-pulmonary tissue; and

(b) causing the mammal to inhale a therapeutically effective amount of gaseous nitric oxide
10 sufficient to diminish the ability of the mammal's leukocytes or platelets to become activated in a manner that contributes to an inflammatory process at the site of the ischemia-reperfusion in the non-pulmonary tissue, thereby lessening or preventing non-pulmonary ischemia-
15 reperfusion injury in the mammal.

2. The method of claim 1, further comprising the step of administering to the mammal a therapeutically effective amount of a second compound that potentiates the therapeutic effect of gaseous nitric oxide.

20 3. The method of claim 2, wherein the second compound is selected from the group consisting of a phosphodiesterase inhibitor and superoxide dismutase.

4. The method of claim 3, wherein the phosphodiesterase inhibitor is selected from the group
25 consisting of 2-o-propoxyphenyl-8-azapurin-6-one, dipyridamole, theophylline, sildenafil, and 1,3-dimethyl-6-(2-propoxy-5-methanesulphonylamidophenyl)-pyrazolo[3,4-D]pyrimidin-4-(5H)-one.

5. The method of claim 2, wherein the second
30 compound is selected from the group consisting of aspirin, ticlopidine, streptokinase, urokinase, t-PA and

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analogues thereof, heparin, and hirudin and analogues thereof.

6. The method of claim 1, wherein the injury is caused by surgery.

5 7. The method of claim 6, wherein the surgery is transplantation surgery.

8. The method of claim 7, wherein the transplantation surgery is kidney transplantation surgery or heart transplantation surgery.

10 9. The method of claim 6, wherein the surgery is heart bypass surgery.

10. The method of claim 1, wherein the injury is caused by a vascular interventional procedure.

15 11. The method of claim 10, wherein the vascular interventional procedure is angioplasty.

12. The method of claim 11, wherein the angioplasty includes the use of a laser, balloon, or stent.

20 13. The method of claim 11, wherein the angioplasty is an atherectomy.

14. The method of claim 10, wherein the vascular interventional procedure is percutaneous transluminal coronary angioplasty.

25 15. The method of claim 1, wherein the injury is caused by thrombolysis.

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16. The method of claim 1, wherein the injury is caused by a stroke.

17. The method of claim 1, wherein the injury occurs in the kidney.

5 18. The method of claim 1, wherein the injury occurs in the heart.

19. The method of claim 1, wherein the injury occurs in the brain.

20. The method of claim 1, wherein the injury
10 occurs spontaneously.

21. The method of claim 1, wherein the therapeutically effective amount of nitric oxide is administered to the mammal at a predetermined concentration range.

15 22. The method of claim 21, wherein the concentration range is 0.1 ppm to 300 ppm.

23. The method of claim 1, wherein the nitric oxide is inhaled continuously for an extended period.

24. The method of claim 1, wherein the nitric
20 oxide is inhaled intermittently for an extended period.

25. The method of claim 1, wherein the mammal is a human.

26. The method of claim 1, wherein the amount of gaseous nitric oxide is sufficient to diminish the
25 ability of platelets to become activated in a manner that

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contributes to the inflammation process at the site of the ischemia-reperfusion.

27. A method for decreasing or preventing non-pulmonary inflammation in a mammal, comprising the steps
5 of:

(a) identifying a mammal which has existing inflammation or is at risk for developing inflammation in a non-pulmonary tissue;

(b) causing the mammal to inhale a
10 therapeutically effective amount of gaseous nitric oxide sufficient to diminish the ability of the mammal's leukocytes or platelets to become activated in a manner that contributes to an inflammation process in the non-pulmonary tissue, thereby decreasing or preventing non-
15 pulmonary inflammation in the mammal; and

(c) immediately before, during, or after the inhalation of nitric oxide by the mammal, administering to the mammal a therapeutically effective amount of a second compound that potentiates the therapeutic effect
20 of gaseous nitric oxide.

28. The method of claim 27, wherein the non-pulmonary inflammation is arthritis, myocarditis, encephalitis, transplant rejection, systemic lupus erythematosus, gout, dermatitis, inflammatory bowel
25 disease, hepatitis, or thyroiditis.

29. The method of claim 27, wherein the second compound is selected from the group consisting of a phosphodiesterase inhibitor and superoxide dismutase.

30. The method of claim 29, wherein the
30 phosphodiesterase inhibitor is selected from the group consisting of 2-o-propoxyphenyl-8-azapurin-6-one,

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dipyridamole, theophylline and 1,3-dimethyl-6-(2-propoxy-5-methanesulphonylamidophenyl)-pyrazolo[3,4-D]pyrimidin-4-(5H)-one.

31. The method of claim 27, wherein the second
5 compound is selected from the group consisting of a non-steroidal anti-inflammatory agent, a glucocorticoid, and a cytotoxic agent.

32. The method of claim 27, wherein the nitric oxide is inhaled in a predetermined concentration range.

10 33. The method of claim 32, wherein the concentration range is 0.1 ppm to 300 ppm.

34. The method of claim 27, wherein the nitric oxide is inhaled continuously for an extended period.

35. The method of claim 27, wherein the nitric
15 oxide is inhaled intermittently for an extended period.

36. The method of claim 27, wherein the mammal is a human.

37. The method of claim 27, wherein the amount of gaseous nitric oxide is sufficient to diminish the
20 ability of platelets to become activated in a manner that contributes to the inflammation process.

38. The method of claim 1, wherein the injury is caused by trauma.

39. The method of claim 1, wherein the injury is
25 caused by temporary hypotension.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/22044

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/12, 9/72, 31/155, 31/195, 31/27, 31/52, 33/00, 33/08

US CL :424/718

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/718

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,427,797 A (FROSTELL et al) 27 June 1995, col. 2, lines 7-18, and 28-37.	1 and 6-26
X	US 5,570,683 A (ZAPOL) 05 November 1996, see entire document.	1-4, 6-30, and 32-39
X	US 5,485,827 A (ZAPOL et al) 23 January 1996, see entire document.	1-4, and 6-39
X,P	US 5,703,073 A (GARVEY et al) 30 December 1997, see entire document.	5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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